

invention relates generally to compositions and methods useful for treating conditions associated with defects in cell proliferation, cell differentiation, and cell survival. The invention is more particularly related to double-stranded RNA polynucleotides that interfere with expression of protein tyrosine phosphatases, and polypeptide variants thereof. The invention is also particularly related to double-stranded RNA polynucleotides that interfere with expression of MAP kinases and MAP kinase kinases and chemotherapeutic target polypeptides, and polypeptide variants thereof. The present invention is also related to the use of such RNA polynucleotides to alter activation of signal transduction pathway components or to alter cellular metabolic processes that lead to proliferative responses, cell differentiation and development, and cell survival.

#### Summary of Invention Paragraph:

[0022] RNA interference (RNAi) is a polynucleotide sequence-specific, post-transcriptional gene silencing mechanism effected by double-stranded RNA that results in degradation of a specific messenger RNA (mRNA), ~~thereby reducing the expression of a desired target polypeptide encoded by the mRNA~~ (see, e.g., WO 99/32619; WO 01/75164; U.S. Pat. No. 6,506,559; Fire et al., Nature 391:806-11 (1998); Sharp, Genes Dev. 13:139-41 (1999); Elbashir et al. Nature 411:494-98 (2001); Harborth et al., J. Cell Sci. 114:4557-65 (2001)). RNAi is mediated by double-stranded polynucleotides as also described hereinbelow, for example, double-stranded RNA (dsRNA), having sequences that correspond to exonic sequences encoding portions of the polypeptides for which expression is compromised. RNAi reportedly is not effected by double-stranded RNA polynucleotides that share sequence identity with intronic or promoter sequences (Elbashir et al., 2001). RNAi pathways have been best characterized in *Drosophila* and *Caenorhabditis elegans*, but "small interfering RNA" (siRNA) polynucleotides that interfere with expression of specific polypeptides in higher eukaryotes such as mammals (including humans) have also been considered (e.g., Tuschl, 2001 Chembiochem. 2:239-245; Sharp, 2001 Genes Dev. 15:485; Bernstein et al., 2001 RNA 7:1509; Zamore, 2002 Science 296:1265; Plasterk, 2002 Science 296:1263; Zamore 2001 Nat. Struct. Biol. 8:746; Matzke et al., 2001 Science 293:1080; Scadden et al., 2001 EMBO Rep. 2:1107).

#### Summary of Invention Paragraph:

[0023] According to a current non-limiting model, the RNAi pathway is initiated by ATP-dependent, processive cleavage of long dsRNA into double-stranded fragments of about 18-27 (e.g., 19, 20, 21, 22, 23, 24, 25, 26, etc.) nucleotide base pairs in length, called small interfering RNAs (siRNAs) (see review by Hutvagner et al., Curr. Opin. Gen. Dev. 12:225-32 (2002); Elbashir et al., 2001; Nyknen et al., Cell 107:309-21 (2001); Zamore et al., Cell 101:25-33 (2000); Bass, Cell 101:235-38 (2000)). In *Drosophila*, an enzyme known as "Dicer" cleaves the longer double-stranded RNA into siRNAs; Dicer belongs to the RNase III family of dsRNA-specific endonucleases (WO 01/68836; Bernstein et al., Nature 409:363-66 (2001)). Further according to this non-limiting model, the siRNA duplexes are incorporated into a protein complex, followed by ATP-dependent unwinding of the siRNA, which then generates an active RNA-induced silencing complex (RISC) (WO 01/68836). The complex recognizes and cleaves a target RNA that is complementary to the guide strand of the siRNA, thus interfering with expression of a specific protein (Hutvagner et al., supra).

#### Summary of Invention Paragraph:

[0024] In *C. elegans* and *Drosophila*, RNAi may be mediated by long double-stranded RNA polynucleotides (WO 99/32619; WO 01/75164; Fire et al., 1998; Clemens et al., Proc. Natl. Acad. Sci. USA 97:6499-6503 (2000); Kisielow et al., Biochem. J. 363:1-5 (2002); see also WO 01/92513 (RNAi-mediated silencing in yeast)). In mammalian cells, however, transfection with long dsRNA polynucleotides (i.e., greater than 30 base pairs) leads to activation of a non-specific sequence response that globally blocks the initiation of protein synthesis and causes mRNA degradation (Bass, Nature 411:428-29 (2001)). Transfection of human and other mammalian cells with double-stranded RNAs of about 18-27 nucleotide base pairs in length interferes in a sequence-specific manner with expression of